(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 400 971 B1

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
29.07.1998 Bulletin 1998/31

(51) Int Cl.[6]: **C07D 205/08**, C07D 305/14

(21) Application number: **90305845.1**

(22) Date of filing: **30.05.1990**

(54) **Method for preparation of taxol**

Verfahren zur Herstellung von Taxol

Méthode de préparation du taxol

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(30) Priority: **31.05.1989 US 359634**
29.09.1989 US 415028

(43) Date of publication of application:
05.12.1990 Bulletin 1990/49

(73) Proprietor: **FLORIDA STATE UNIVERSITY**
Tallahassee, Florida (US)

(72) Inventor: **Holton, Robert A**
Tallahassee, Florida (US)

(74) Representative: **Eyles, Christopher Thomas et al**
W.P. THOMPSON & CO.
Celcon House
289-293 High Holborn
London WC1V 7HU (GB)

(56) References cited:
- **JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 110, 1988, pages 5.917-5.919, Washington, US; J.-N. DENIS et al.: "A highly efficient, practical approach to natural taxol"**

EP 0 400 971 B1

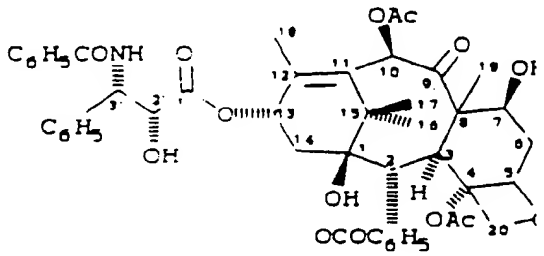
Printed by Jouve, 75001 PARIS (FR)

Description

BACKGROUND OF THE INVENTION

The present invention is directed to novel β-lactams, a process for their preparation, and a process for the preparation of taxol involving the use of such β-lactams.

The taxane family of terpenes, of which taxol is a member, has attracted considerable interest in both the biological and chemical arts. Taxol is a promising cancer chemotherapeutic agent with a broad spectrum of antileukemic and tumor-inhibiting activity, having the following structure:

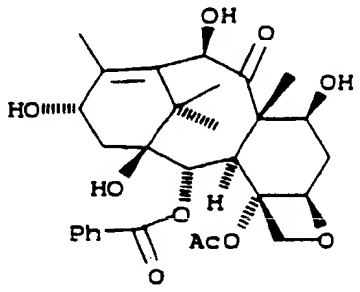


Because of this promising activity, taxol is currently undergoing clinical trials in both France and the United States.

The supply of taxol for these clinical trials is presently being provided by the bark from several species of yew. However, taxol is found only in minute quantities in the bark of these slow growing evergreens, causing considerable concern that the limited supply of taxol will not meet the demand. Consequently, chemists in recent years have expended their energies in trying to find a viable synthetic route for the preparation of taxols. So far, the results have not been entirely satisfactory.

One synthetic route that has been proposed is directed to the synthesis of the tetracyclic taxane nucleus from commodity chemicals. A synthesis of the taxol congener taxusin has been reported by Holton, et al. in JACS 110, 6558 (1988). Despite the progress made in this approach, the final total synthesis of taxol is, nevertheless, likely to be a multi-step, tedious, and costly process.

An alternate approach to the preparation of taxol has been described by Greene, et al. in JACS 110, 5917 (1988), and involves the use of a congener of taxol, 10-deacetyl baccatin III which has the structure shown below:



10-deacetyl baccatin III is more readily available than taxol since it can be obtained from the leaves of Taxus baccata. According to the method of Greene et al., 10-deacetyl baccatin III is converted to taxol by attachment of the C10 acetyl group and by attachment of the C13 β-amido ester side chain through the esterification of the C-13 alcohol with a β-amido carboxylic acid unit. Although this approach requires relatively few steps, the synthesis of the β-amido carboxylic acid unit is a multi-step process which proceeds in low yield, and the coupling reaction is tedious and also proceeds in low yield. However, this coupling reaction is a key step which is required in every contemplated synthesis of taxol or biologically active derivative of taxol, since it has been shown by Wani, et al. in JACS 93, 2325 (1971) that the presence of the 13-amido ester side chain at C13 is required for anti-tumor activity.

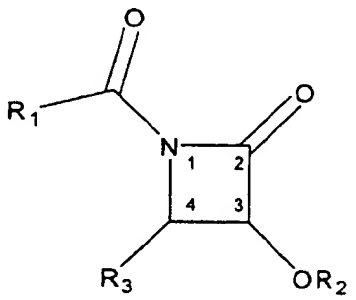
A major difficulty remaining in the synthesis of taxol and other potential anti-tumor agents is the lack of a readily

available unit which could be easily attached to the C13 oxygen to provide the β-amido ester side chain. Development of such a unit and a process for its attachment in high yield would facilitate the synthesis of taxol as well as related anti-tumor agents having a modified set of nuclear substituents or a modified C13 side chain. This need has been fulfilled by the discovery of a new, readily available, side chain precursor chemical unit and an efficient process for its attachment at the C13 oxygen.

SUMMARY OF THE INVENTION

Among the objects of the present invention, therefore, is the provision of a side chain precursor for the synthesis of taxols, and the provision of a process for the attachment of the side chain precursor in relatively high yield to provide a taxol intermediate.

Briefly, therefore, the present invention is directed to a side chain precursor, a β-lactam 1 of the formula:



1

wherein R_1 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; R_2 is ethoxyethyl, 2,2,2-trichloroethoxymethyl or other hydroxyl protecting group; and R_3 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; and wherein any alkyl group present may be substituted or unsubstituted and contains from 1 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, any alkenyl or alkynyl group present may be substituted or unsubstituted and contains from 2 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, and any aryl or substituted aryl group present contains from 6 to 15 carbon atoms; enantiomers and diastereoisomers thereof.

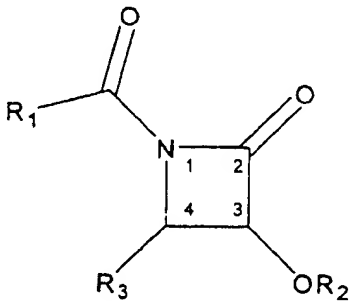
The present invention is also directed to a process for the preparation of a taxol intermediate comprising contacting an alcohol with β-lactam 1 in the presence of a sufficient amount of an activating agent under effective conditions to cause the β-lactam to react with the alcohol to form a β-amido ester which may be used as an intermediate in the synthesis of a taxol.

The present invention is also directed to a process for the preparation of a taxol which comprises contacting an alcohol with β-lactam 1 in the presence of a sufficient amount of an activating agent under effective conditions to cause the β-lactam to react with the alcohol to form a β-amido ester taxol intermediate. The intermediate is then used in the synthesis of a taxol.

Other objects and features of this invention will be in part apparent and in part pointed out hereinafter.

DETAILED DESCRIPTION

The present invention is directed to a β-lactam 1 and its derivatives, the structure of which is depicted hereinbelow.

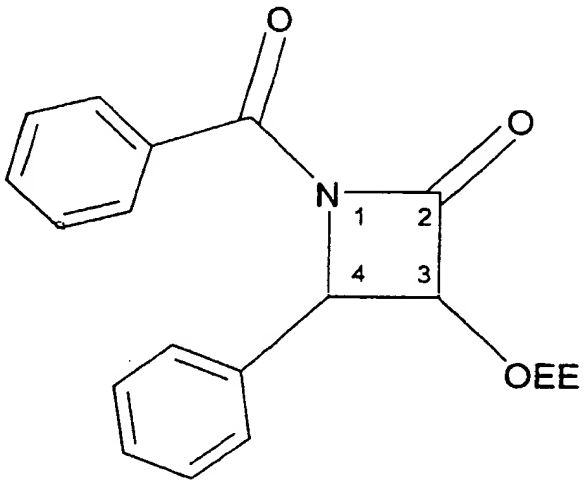


1

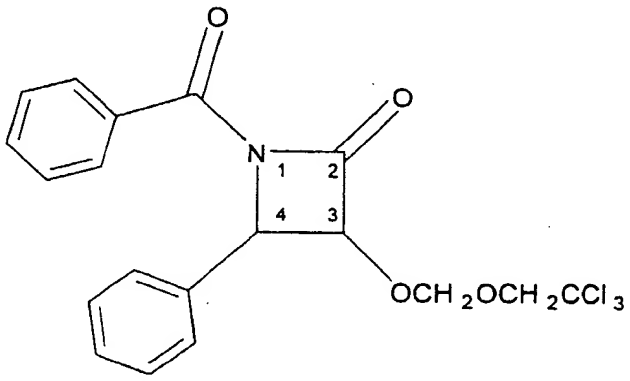
As noted above, R_1 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; R_2 is ethoxyethyl, 2,2,2-trichloroethoxymethyl or other hydroxyl protecting group; and R_3 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxyl halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; and wherein any alkyl group present may be substituted or unsubstituted and contains from 1 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, any alkenyl or alkynyl group present may be substituted or unsubstituted and contains from 2 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, and any aryl or substituted aryl group present contains from 6 to 15 carbon atoms; enantiomers and diastereoisomers thereof. Preferably, R_1 is phenyl, phenyl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido, or aryl; R_2 is ethoxyethyl.

P and Q are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or P and Q together form an oxo; and

2,2,2-trichloroethoxymethyl, or other acetal hydroxyl protecting group; and R_3 is phenyl, phenyl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido, or aryl. Structures of two of the preferred β-lactams in which R_1 and R_3 are phenyl, are shown below:



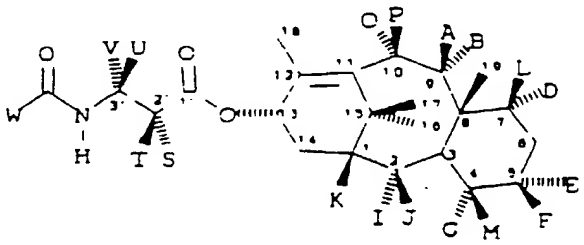
2



3

According to IUPAC rules, the names of β-lactams **2** and **3** are 1-Benzoyl-4-phenyl-3-(1-ethoxyethoxy)azetidin-2-one **2**, and 1-Benzoyl-4-phenyl-3-(2,2,2-trichloroethoxymethoxyazetidin-2-one **3**. The most preferred β-lactam is β-lactam **2**.

In accordance with the present invention, a process is provided for preparing taxol intermediates, natural taxol and non-naturally occurring taxols having the following structural formula:



4

wherein

A and B are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
A and B together form an oxo;
L and D are independently hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy;
E and F are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or;
E and F together form an oxo;
G is hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
G and M together form an oxo or methylene or
G and M together form an oxirane ring or
M and F together form an oxerane ring;
J is hydrogen, hydroxy, or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
I is hydrogen, hydroxy, or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or
I and J taken together form an oxo; and
K is hydrogen, hydroxy or lower alkoxy, alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; and
S is hydroxy;
T is hydrogen;
U and V are independently hydrogen or alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent

selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; and
W is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido;
and wherein any alkyl group present may be substituted or unsubstituted and contains from 1 to 6 carbon atoms in the principal chain and up to 10 carbon atoms in total, any alkenyl or alkynyl group present may be substituted or unsubstituted and contains from 2 to 6 carbon atoms in the principal chain and up to 10 carbon atoms in total, and any aryl or substituted aryl group present contains from 6 to 10 carbon atoms;
comprising:
contacting a β-lactam 1 with an alcohol, the contacting of said β-lactam and said alcohol being carried out in the presence of a sufficient amount of an activating agent under effective conditions to cause the β-lactam to react with the alcohol to form a β-amido ester which is suitable for use as an intermediate in the synthesis of a taxol, and converting said intermediate to the taxol.

The taxol alkyl groups, either alone or with any substitutent, are alkyl containing from one to six carbon atoms in the principal chain and up to 10 carbon atoms in total. They may be straight or branched chain and include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, amyl, and hexyl.

The taxol alkenyl groups, either alone or with any substituent, are alkenyl containing from two to six carbon atoms in the principal chain and up to 10 carbon atoms in total. They may be straight or branched chain and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, and hexenyl.

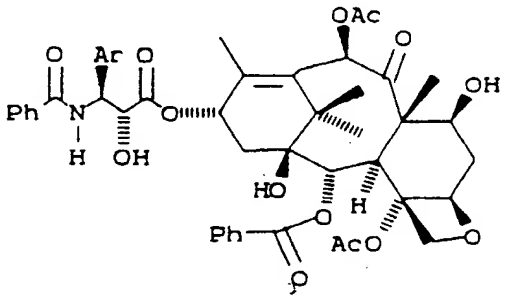
The taxol alkynyl groups, either alone or with any substituent, are alkynyl containing from two to six carbon atoms in the principal chain and up to 10 carbon atoms in total. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, pentynyl, and hexynyl.

Exemplary alkanoyloxy include acetate, propionate, butyrate, valerate, and isobutyrate. The more preferred alkanoyloxy is acetate.

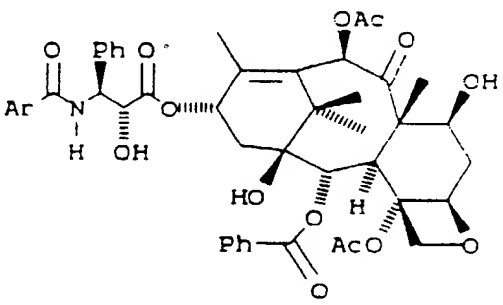
The taxol aryl moieties, either alone or with various substituents contain from 6 to 10 carbon atoms and include phenyl, α-naphthyl or β-naphthyl, Substituents are chosen from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino, and amido. Phenyl is the more preferred aryl.

Preferred compounds of the generic formula include those in which substituent G is H, substituent M is CH_2O (forming an oxetane ring with substituent F), substituent U is R and substituent V is H.

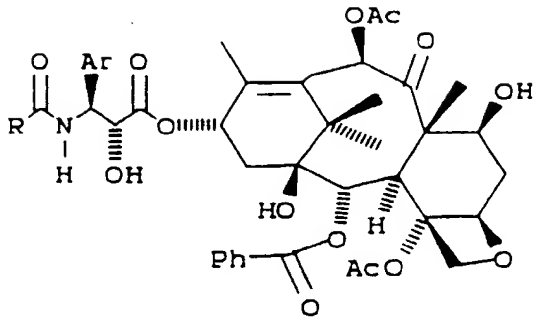
Exemplary compounds within the generic formula are depicted hereinbelow:



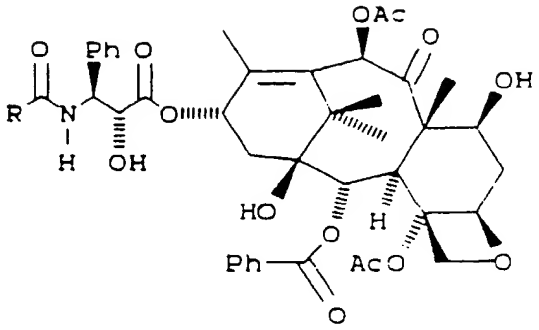
5



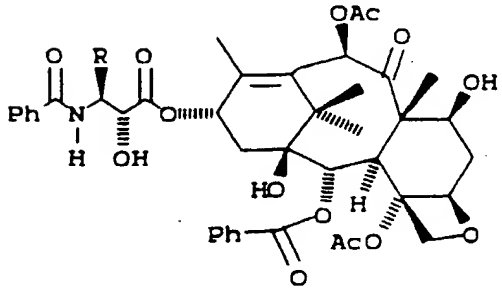
6



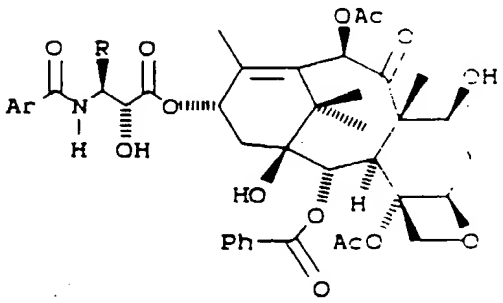
7



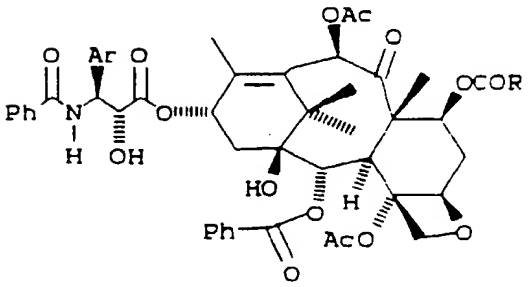
8



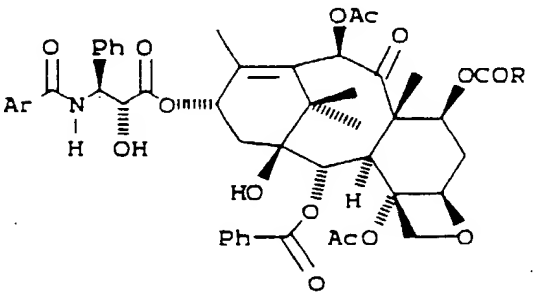
9



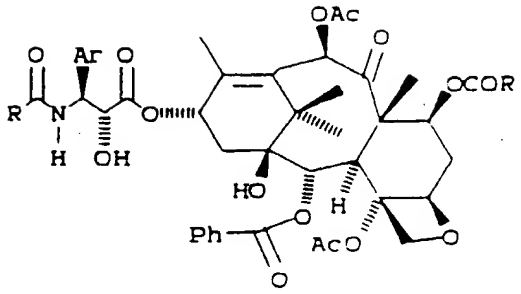
10



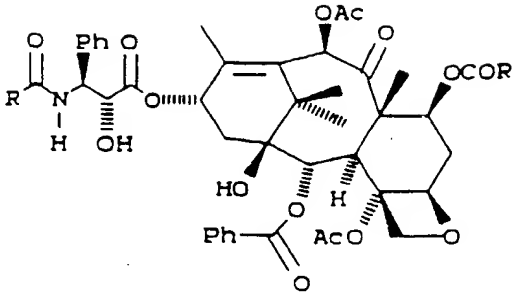
11



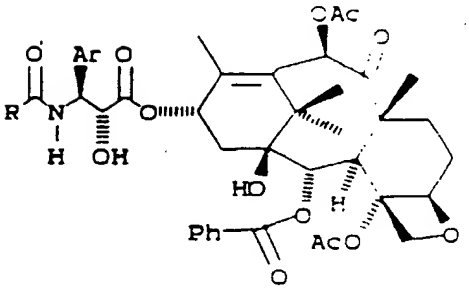
12



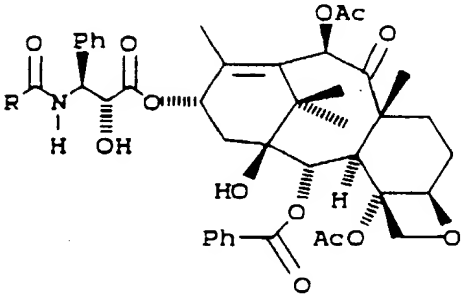
13



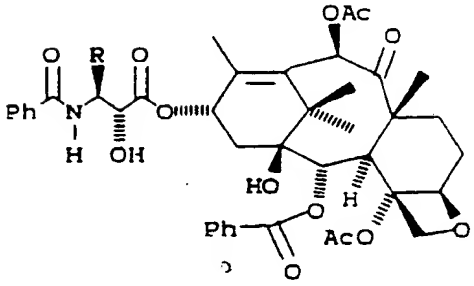
14



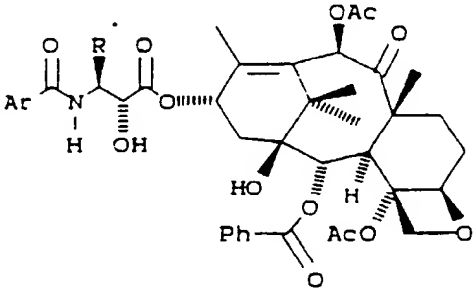
15



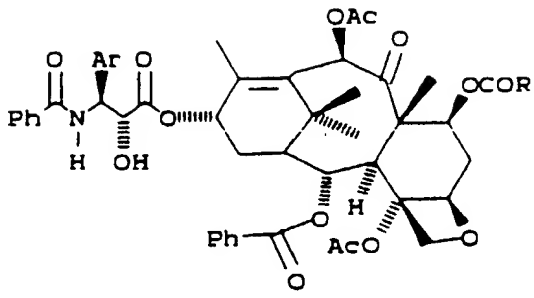
16



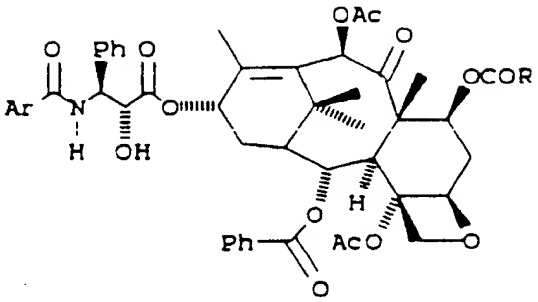
17



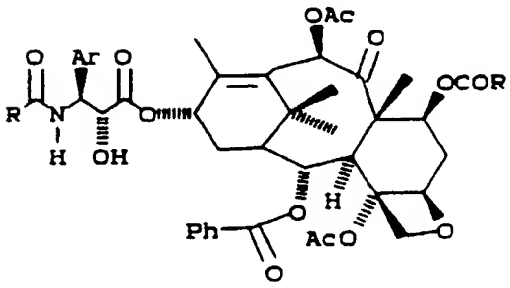
18



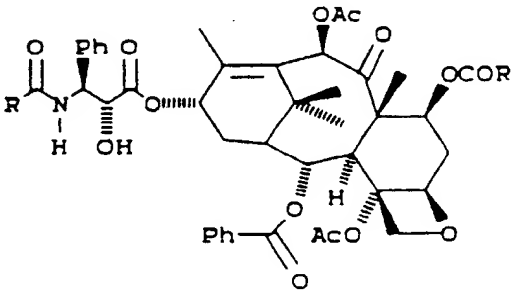
19



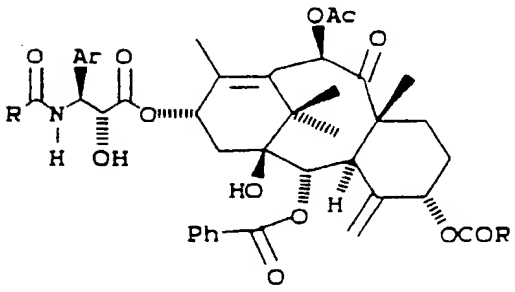
20



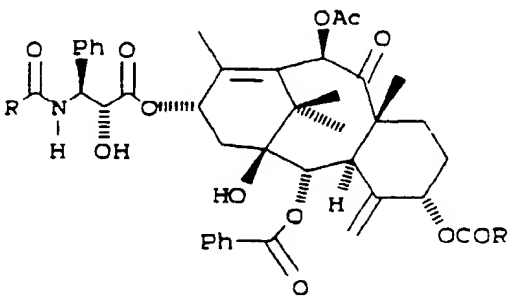
21



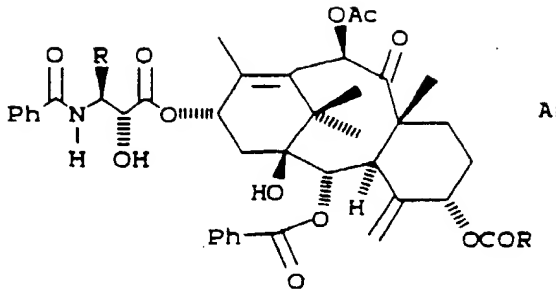
22



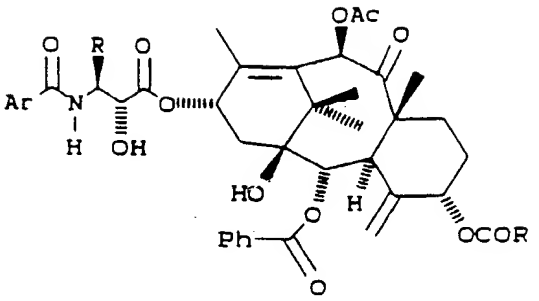
23



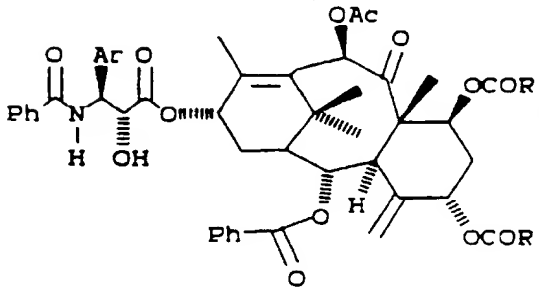
24



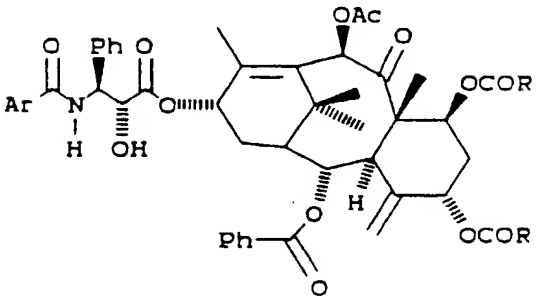
25



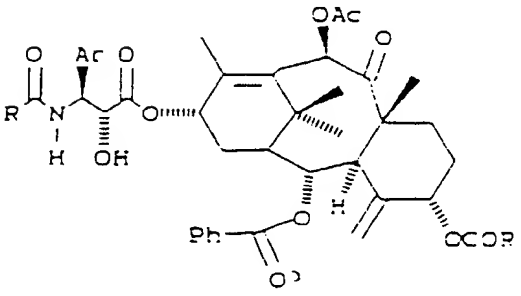
26



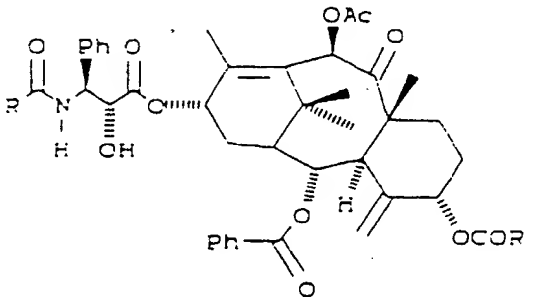
27



28



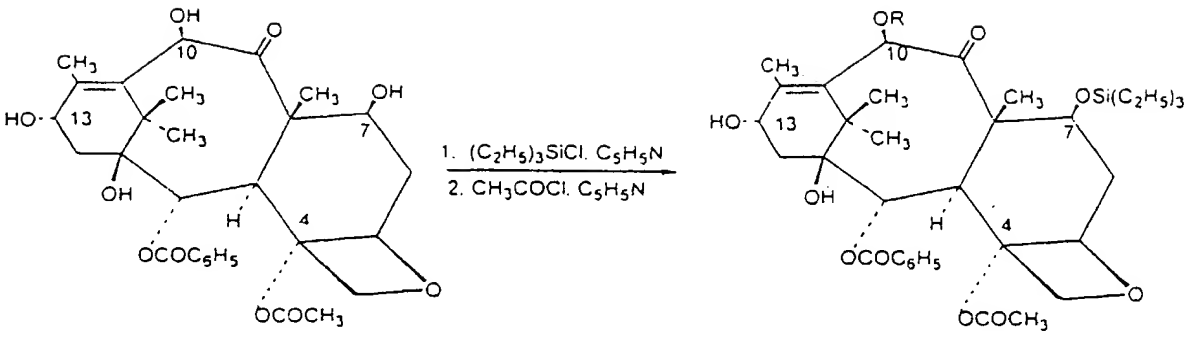
29



30

In accordance with the process of the present invention, β-lactams **1** are converted to β-amido esters in the presence of an alcohol and an activating agent, preferably a tertiary amine such as triethyl amine, diisopropyl ethyl amine, pyridine, N-methyl imidizole, and 4-dimethylaminopyridine (DMAP). For example, β-lactams **1** react with compounds having the taxane tetracyclic nucleus and a C13 hydroxyl group, in the presence of 4-dimethylaminopyridine (DMAP), to provide substances having a β-amido ester group at C13.

Most preferably, the alcohol is 7-O-triethylsilyl baccatin III which can be obtained as described by Greene, et al. in JACS 110, 5917 (1988) or by other routes. As reported in Greene et al., 10-deacetyl baccatin III is converted to 7-O-triethylsilyl baccatin III according to the following reaction scheme:

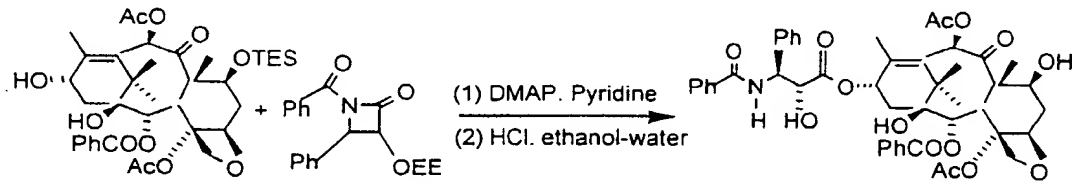


31

32 a. R=H
b. R=$COCH_3$

Under what is reported to be carefully optimized conditions, 10-deacetyl baccatin III is reacted with 20 equivalents of $(C_2H_5)_3SiCl$ at 23°C under an argon atmosphere for 20 hours in the presence of 50 mL of pyridine/mmol of 10-deacetyl baccatin III to provide 7-triethylsilyl-10-deacetyl baccatin III (32a) as a reaction product in 84-86% yield after purification. The reaction product is then acetylated with 5 equivalents of CH_3COCl and 25 mL of pyridine/mmol of 32a at 0°C under an argon atmosphere for 48 hours to provide 86% yield of 7-0-triethylsilyl baccatin III (32b). Greene, et al. in JACS 110, 5917 at 5918 (1988).

As shown in the following reaction scheme, 7-0-triethylsilyl baccatin III 32b may be reacted with a β-lactam of the present invention at room temperature to provide a taxol intermediate in which the C-7 and C-2' hydroxyl groups are protected with triethylsilyl and ethoxyethyl protecting groups, respectively. These groups are then hydrolyzed under mild conditions so as not to disturb the ester linkage or the taxol substituents.



32b

TAXOL

Although the present scheme is directed to the synthesis of the natural product taxol, it can be used with modifications in either the β-lactam or the tetracyclic alcohol, which can be derived from natural or unnatural sources, to prepare other synthetic taxols contemplated within the present invention.

Alternatively, a β-lactam 1 may be converted to a β-amido ester in the presence of an activating agent and an alcohol other than 7-O-triethylsilyl baccatin III to form a taxol intermediate. Synthesis of taxol may then proceed using the taxol intermediate under an appropriate reaction scheme.

The β-lactam alkyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkyl containing from one to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, amyl, hexyl, and the like.

The β-lactam alkenyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkenyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, pentenyl, hexenyl, and the like.

The β-lactam alkynyl groups, either alone or with the various substituents defined hereinabove are preferably lower alkynyl containing from two to six carbon atoms in the principal chain and up to 15 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, pentynyl , hexynyl, and the like.

Exemplary β-lactam alkanoyloxy include acetate, propionate, butyrate, valerate, and isobutyrate. The more preferred alkanoyloxy is acetate.

The β-lactam aryl moieties described, either alone or with various substituents contain from 6 to 15 carbon atoms

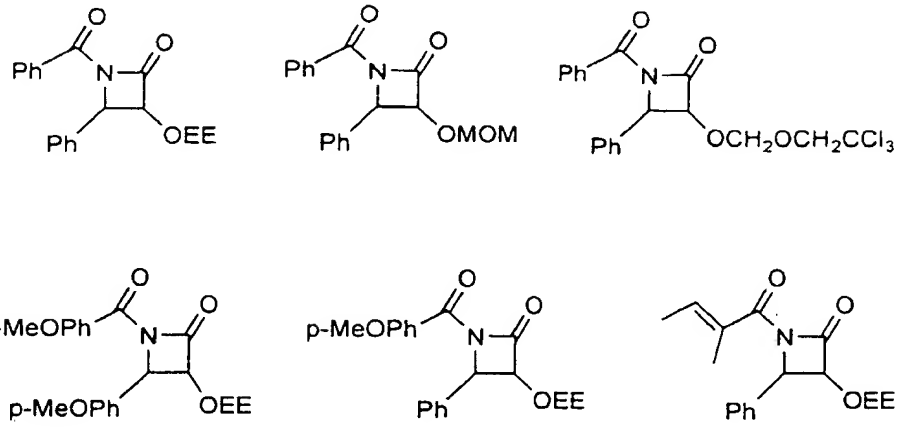
and include phenyl, α-naphthyl or β-naphthyl, etc. Substituents include alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino, and amido, Phenyl is the more preferred aryl.

As noted above, R_2 of β-lactam 1 may be alkyl, acyl, ethozyethyl, 2,2,2-trichloroethoxymethyl, or other hydroxyl protecting group such as acetals and ethers, i.e., methoxymethyl, benzyloxymethyl; esters, such as acetates; carbonates, such as methyl carbonates; and the like. A variety of protecting groups for the hydroxyl group and the synthesis thereof may be found in "Protective Groups in Organic Synthesis" by T. W. Greene, John Wiley and Sons, 1981. The hydroxyl protecting group selected should be easily removed under conditions that are sufficiently mild so as not to disturb the ester linkage or other substituents of the taxol intermediate. However, R_2 is preferably ethoxyethyl or 2,2,2-trichloroethoxymethyl, and most preferably ethoxyethyl.

Preferred values of the β-lactam substituents R_1, R_2, and R_3 are enumerated herein below:

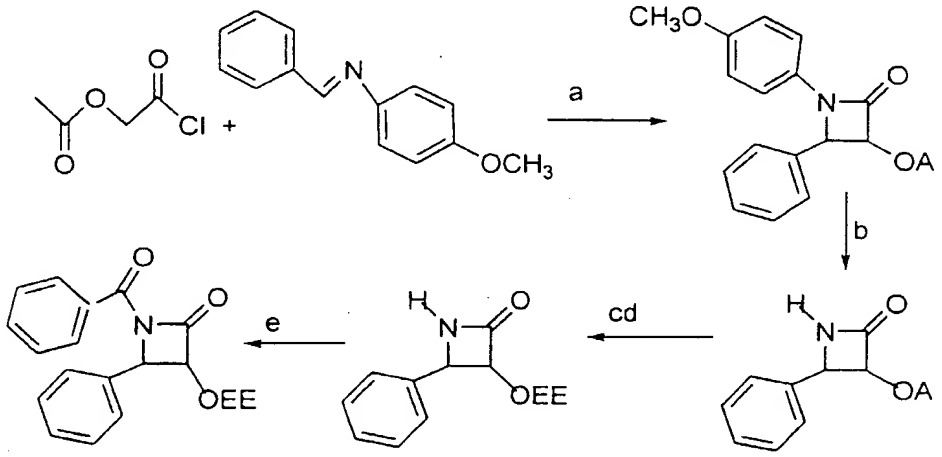
R_1=Ph	R_1=Ar	R_1=p-MeOPh	R_1=alkyl	R_1=alkenyl	R_1=alkynyl	R_1=H
R_2=EE	R_2=SiR_3	R_2=alkyl	R_2=OCOR	R_2=MOM	R_2=$Cl_3CCH_2OCH_2$	
R_3=Ph	R_3=Ar	R_3=p-MeOPh	R_3=alkyl	R_3=alkenyl	R_3=alkynyl	R_3=H

Exemplary compounds within the generic formula are depicted hereinbelow:



Since the β-lactam 1 has several asymmetric carbons, it is known to those skilled in the art that the compounds of the present invention having asymmetric carbon atoms may exist in diastereomeric, racemic, or optically active forms. All of these forms are contemplated within the scope of this invention. More specifically, the present invention includes enantiomers, diastereomers, racemic mixtures, and other mixtures thereof.

The β-lactams 1 can be prepared from readily available materials, as is illustrated for β-lactam 2 in the scheme below:



reagents: (a) triethylamine, CH_2Cl_2, 25°C, 18h; (b) 4 equiv ceric ammonium nitrate, CH_3CN, -10°C, 10 min; (c) KOH, THF, H_2O, 0°C, 30 min; (d) ethyl vinyl ether, THF, toluene sulfonic acid (cat.), 0°C, 1.5h; (e) CH_3Li, ether, -78°C, 10 min; benzoyl chloride, -78°C, 1h.

The starting materials are readily available. α-Acyloxy acetyl chloride is prepared from glycolic acid, and, in the presence of a tertiary amine, it cyclocondenses with imines prepared from aldehydes and p-methoxyaniline to give 1-p-methoxyphenyl-3-acyloxy-4-arylazetidin-2-ones.

The p-methoxyphenyl group can be readily removed through oxidation with ceric ammonium nitrate, and the acyloxy group can be hydrolyzed under standard conditions familiar to those experienced in the art to provide 3-hydroxy-4-arylazetidin-2-ones.

The 3-hydroxyl group may be protected with a variety of standard protecting groups such as the 1-ethoxyethyl group. Preferably, the racemic 3-hydroxy-4-arylazetidin-2-one is resolved into the pure enantiomers prior to protection by recrystallization of the corresponding 2-methoxy-2-(trifluoromethyl) phenylacetic esters and only the dextrorotatory

enantiomer is used in the preparation of taxol. In any event, the 3-(1-ethoxyethoxy)-4-phenylazetidin-2-one can be converted to β-lactam **2**, by treatment with a base, preferably n-butyllithium, and an aroyl chloride at -78 °C or below.

The following examples illustrate the invention.

EXAMPLE 1

PREPARATION OF CIS-1-BENZOYL-3-(1-ETHOXYETHOXY)-4-PHENYLAZETIDINONE 2

cis-1-p-methoxyphenyl-3-acetoxy-4-phenylazetidin-2-one. To a solution of 962 mg (4.56 mmol) of the imine derived from benzaldehyde and p-methoxy aniline, and 0.85 mL (6.07 mmol) of triethylamine in 15 mL of CH_2Cl_2 at -20°C was added dropwise a solution of 413 mg (3.04 mmol) of α-acetoxy acetyl chloride in 15 mL of CH_2Cl_2. The reaction mixture was allowed to warm to 25°C over an 18 h period. The reaction mixture was then diluted with 100 mL of CH_2Cl_2 and the solution was extracted with 30 mL of 10% aqueous HCl. The organic layer was washed with 30 mL of water and 30 mL of saturated aqueous sodium bicarbonate, dried over sodium sulfate, and concentrated to provide a solid mass. The solid was triturated with 50 mL of hexane and the mixture was filtered. The remaining solid was recrystallized from ethyl acetate/hexane to give 645 mg (68%) of cis-1-p-methoxyphenyl-3-acetoxy-4-phenylazetidin-2-one as white crystals, m.p. 163°C.

cis-3-acetoxy-4-phenylazetidin-2-one. To a solution of 20.2 g of cis-1-p-methoxyphenyl-3-acetoxy-4-phenylazetidin-2-one in 700 mL of acetonitrile at -10°C was slowly added a solution of ceric ammonium nitrate in 450 mL of water over a 1 h period. The mixture was stirred for 30 min at -10°C and diluted with 500 mL of ether. The aqueous layer was extracted with two 100 mL portions of ether, and the combined organic layer was washed with two 100 mL portions of water, two 100 mL portions of saturated aqueous sodium bisulfite, two 100 mL portions of saturated aqueous sodium bicarbonate and concentrated to give 18.5 g of a solid. Recrystallization of the solid from acetone/hexane gave 12.3 g (92%) of cis-3-acetoxy-4-phenylazetidin-2-one as white crystals, m.p. 152-154°C.

cis-3-hydroxy-4-phenylazetidin-2-one. To a mixture of 200 mL of THF and 280 mL of 1 M aqueous potassium hydroxide solution at 0°C was added a solution of 4.59 g (22.4 mmol) of cis-3-acetoxy-4-phenylazetidin-2-one in 265 mL of THF via a dropping funnel over a 40 min period. The solution was stirred at 0°C for 1 h and 100 mL of water and 100 mL of saturated sodium bicarbonate were added. The mixture was extracted with four 200 mL portions of ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated to give 3.54 g (97%) of racemic cis-3-hydroxy-4-phenylazetidin-2-one as white crystals, m.p. 147-149°C. This material was resolved into its enantiomers by recrystallization of its 2-methoxy-2- (trifluoromethyl)phenylacetic ester from hexane/acetone followed by hydrolysis, $[\alpha]^{25}_{Hg}177°$.

cis-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one. To a solution of 3.41 g (20.9 mmol) of cis-3-hydroxy-4-phenylazetidin-2-one in 15 mL of THF at 0°C was added 5 mL of ethyl vinyl ether and 20 mg (0.2 mmol) of methanesulfonic acid. The mixture was stirred at 0°C for 20 min, diluted with 20 mL of saturated aqueous sodium bicarbonate, and extracted with three 40 mL portions of ethyl acetate. The combined ethyl acetate layers were dried over sodium sulfate and concentrated to give 4.87 g (99%) of cis-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one as a colorless oil.

cis-1-benzoyl-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one To a solution of 2.35 g (10 mmol) of cis-3-(1- thoxyethoxy)-4-phenylazetidin-2-one in 40 mL of THF at -78°C was added 6.1 mL (10.07 mmol) of a 1.65 M solution of n-butyllithium in hexane. The mixture was stirred for 10 min at -78°C and a solution of 1.42 g (10.1 mmol) of benzoyl chloride in 10 mL of THF was added. The mixture was stirred at -78°C for 1 h and diluted with 70 mL of saturated aqueous sodium bicarbonate and extracted with three 50 mL portions of ethyl acetate. The combined ethyl acetate extracts were dried over sodium sulfate and concentrated to give 3.45 g of an oil. Chromatography of the oil on silica gel eluted with ethyl acetate/hexane gave 3.22 g (95%) of cis-1-benzoyl-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one (2) as a colorless oil.

EXAMPLE 2

PREPARATION OF β-AMIDO ESTERS FROM CIS-1-BENZOYL-3-(1-ETHOXYETHOXY)-4-PHENYLAZETIDIN-2-ONE 2

Benzyl-3-benzamido-3-phenyl-2-hydroxypropionate. To a solution of 88 mg (0.26 mmol) of cis-1-benzoyl-3-(1-ethoxyethoxy)-4-phenylazetidin-2-one in 0.3 mL of THF was added 28 mg (0.26 mmol) of benzyl alcohol and 32 mg (0.26 mmol) of 4-dimethylamino pyridine (DMAP). After 5 h at 25°C the mixture was diluted with 10 mL of saturated aqueous sodium bicarbonate solution and extracted with three 20 mL portions of ethyl acetate. The combined ethyl acetate layers were extracted with 10 mL of 5% aqueous HCl and 10 mL of saturated sodium bicarbonate, dried over sodium sulfate and concentrated to give 112 mg (100%) of benzyl ester as an oil which was >97% pure by NMR analysis. To a solution of this oil in 4 mL of THF was added 1 mL of 10% aqueous HCl solution. The mixture was stirred

at 25°C for 30 min, diluted with 20 mL of saturated aqueous sodium bicarbonate solution, and extracted with four 30 mL portions of ethyl acetate. The combined ethyl acetate extracts were dried over sodium sulfate and concentrated to provide a solid. Recrystallization of the solid from chloroform gave 92 mg (95%) of benzyl-3-benzamido-3-phenyl-2-hydroxypropionate as white crystals, m.p. 129-131°C.

Taxol. To a small reaction vessel was added 109 mg (0.320 mmol) of (+)-cis-1-benzoyl-3-(1-ethoxyethoxy-4-phenyl-azetidin-2-one, 45 mg (0.064 mmol) of 7-O-triethylsilyl baccatin III, 7.8 mg (0.064 mmol) of 4-dimethylamino pyridine (DMAP) and 0.032 mL of pyridine. The mixture was stirred at 25°C for 12 h and diluted with 100 mL of ethyl acetate. The ethyl acetate solution was extracted with 20 mL of 10% aqueous copper sulfate solution, dried over sodium sulfate and concentrated. The residue was filtered through a plug of silica gel and eluted with ethyl acetate. Flash chromatography on silica gel eluted with ethyl acetate/hexane followed by recrystallization from ethyl acetate/hexane gave 61 mg (92%) of 2'-(1-ethoxyethoxy)-7-O-triethylsilyl taxol as a 2:1 mixture of diastereomers.

A 5 mg sample of 2'-(1-ethoxyethoxy)-7-O-triethylsilyl taxol was dissolved in 2 mL of ethanol and 0.5 mL of 0.5% aqueous HCl solution was added. The mixture was stirred at 0°C for 30 h and diluted with 50 mL ethyl acetate. The solution was extracted with 20 mL of saturated aqueous sodium bicarbonate solution, dried over sodium sulfate and concentrated. The residue was purified by column chromatography on silica gel eluted with ethyl acetate/hexane to provide 4.5 mg. (ca. 90%) of taxol, which was identical with an authentic sample in all respects.

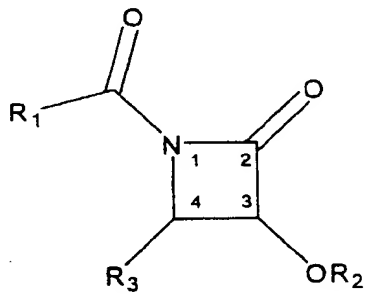
In view of the above, it will be seen that the several objects of the invention are achieved.

As various changes could be made in the above compositions and processes without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense.

Claims

Claims for the following Contracting States : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. A β-lactam of the formula:



1

wherein R_1 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; R_2 is ethoxyethyl, 2,2,2-trichloroethoxymethyl or other hydroxyl protecting group; and R_3 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; and wherein any alkyl group present may be substituted or unsubstituted and contains from 1 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, any alkenyl or alkynyl group present may be substituted or unsubstituted and contains from 2 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, and any aryl or substituted aryl group present contains from 6 to 15 carbon atoms; enantiomers and diastereoisomers thereof.

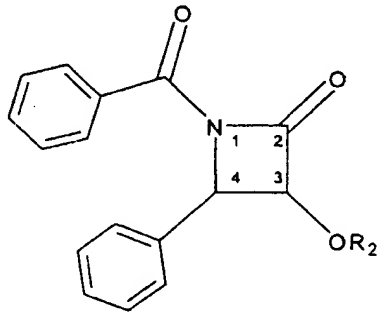
2. A β-lactam according to claim 1, wherein R_1 is phenyl, phenyl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido, or aryl; R_2 is ethoxyethyl, or

2,2,2-trichloroethoxymethyl; and R_3 is phenyl, phenyl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido, or aryl.

3. A β-lactam according to claim 1 or claim 2, wherein R_2 is ethoxyethyl.

4. A β-lactam according to any one of claims 1 to 3, wherein R_1 is alkenyl or alkynyl.

5. A β-lactam of the formula:

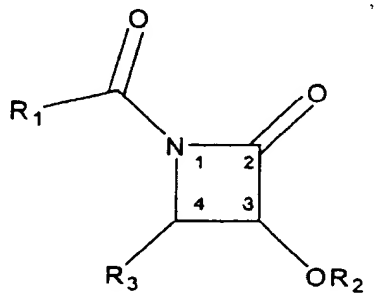


wherein R_2 is a hydroxyl protecting group.

6. A β-lactam according to any one of claims 1 to 5, wherein R_2 is selected from acetals, ethers, esters, and carbonates.

7. A β-lactam according to any one of claims 1 to 6, wherein R_3 is alkyl or alkynyl.

8. A process for the preparation of a taxol intermediate comprising contacting an alcohol with a β-lactam having the formula:



wherein

R_1 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido;
R_2 is a hydroxyl protecting group and
R_3 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; and wherein any alkyl group present may be substituted or unsubstituted and contains from 1 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, any alkenyl or alkynyl group present may be substituted or unsubstituted and contains from 2 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, and any aryl or substituted aryl group present contains from 6 to 15 carbon atoms; or an enantiomer or diastereoisomer thereof,

the contacting of said alcohol and β-lactam being carried out in the presence of a sufficient amount of an activating agent under effective conditions to cause the β-lactam to react with the alcohol to form a β-amido ester which is suitable for use as an intermediate in the synthesis of taxol.

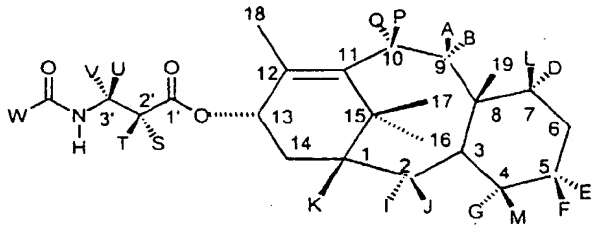
9. A process for the preparation of taxol which comprises preparing a taxol intermediate by a process according to claim 8 and converting said intermediate to taxol.

10. A process according to claims 8 or claim 9, wherein the hydroxyl protecting group is selected from acetals, ethers, esters, and carbonates.

11. A process according to any one of claims 8 to 10, wherein R_1 is aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; R_2 is ethoxyethyl or 2,2,2-trichloroethoxymethyl; and R_3 is aryl or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido.

12. A process according to any one of claims 8 to 11, wherein R_2 is ethoxyethyl.

13. A process for the preparation of a taxol having the formula:



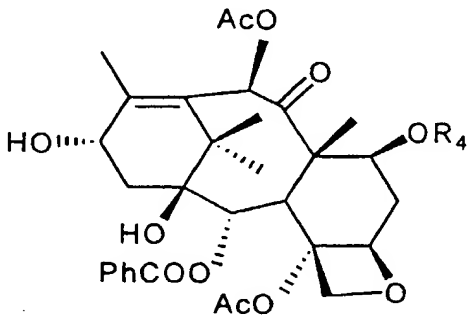
wherein

A and B are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
A and B together form an oxo;
L and D are independently hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy;
E and F are independently hydrogen or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or;
E and F together form an oxo;
G is hydrogen or hydroxy or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
G and M together form an oxo or methylene or
G and M together form an oxirane ring or
M and F together form an oxetane ring;
J is hydrogen, hydroxy, or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
I is hydrogen, hydroxy, or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or
I and J taken together form an oxo; and
K is hydrogen, hydroxy or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; and
P and Q are independently hydrogen or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
P and Q together form an oxo;
S is hydroxy;
T is hydrogen;
U and V are independently hydrogen or alkyl, alkenyl, alkynyl, aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; and
W is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido;
and wherein any alkyl group present may be substituted or unsubstituted and contains from 1 to 6 carbon atoms in the principal chain and up to 10 carbon atoms in total, any alkenyl or alkynyl group present may be substituted or unsubstituted and contains from 2 to 6 carbon atoms in the principal chain and up to 10 carbon atoms in total, and any aryl or substituted aryl group present contains from 6 to 10 carbon atoms;

comprising:

contacting a β-lactam according to any one of claims 1 to 5 with an alcohol, the contacting of said β-lactam and said alcohol being carried out in the presence of a sufficient amount of an activating agent under effective conditions to cause the β-lactam to react with the alcohol to form a β-amido ester which is suitable for use as an intermediate in the synthesis of taxol, and converting said intermediate to taxol.

14. A process according to any one of claims 8 to 13, wherein the alcohol has the formula:



wherein R_4 is a hydroxyl protecting group, Ph is phenyl and Ac is acetyl.

15. A process according to claim 14, wherein R_4 is selected from ethers, esters, carbonates and silyl groups.

16. A process according to claim 14 or claim 15, wherein R_4 is ethoxyethyl, trimethyl silyl or triethyl silyl.

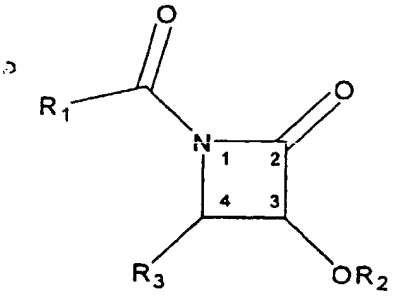
17. A process according to any one of claims 8 to 16, wherein said R_1 is phenyl and said R_3 is phenyl.

18. A process according to any one of claims 8 to 17, wherein the activating agent is a tertiary amine.

19. A process according to claim 18, wherein the activating agent is triethyl amine, diisopropyl ethyl amine, pyridine, N-methyl imidazole, or 4-dimethylaminopyridine.

Claims for the following Contracting States : ES, GR

1. A process for the production of a β-lactam of the formula:



1

wherein R_1 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; R_2 is ethoxyethyl, 2,2,2-trichlo-

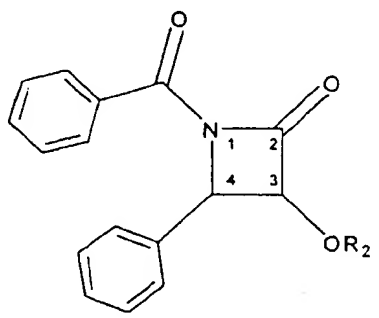
roethoxymethyl or other hydroxyl protecting group; and R_3 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; and wherein any alkyl group present may be substituted or unsubstituted and contains from 1 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, any alkenyl or alkynyl group present may be substituted or unsubstituted and contains from 2 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, and any aryl or substituted aryl group present contains from 6 to 15 carbon atoms; an enantiomer or diastereoisomer thereof, which process comprises cyclocondensing an α-acyloxyacetyl chloride with an imine in the presence of a tertiary amine, said imine being the reaction product of an aldehyde of formula R_3CHO and p-methoxyaniline, to form a 1-p-methoxyphenyl-3-acyloxy-4-arylazetidin-2-one, and removing the p-methoxyphenyl group by oxidation with ceric ammonium nitrate, followed by hydrolysis to convert the 3-acyloxy group to a 3-hydroxy group, and protecting the 3-hydroxy group thereby to convert it to a 3-OR_2 group.

2. A process according to claim 1, wherein R_1 is phenyl, phenyl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido, or aryl; R_2 is ethoxyethyl, or 2,2,2-trichloroethoxymethyl; and R_3 is phenyl, phenyl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido, or aryl.

3. A process according to claim 1 or claim 2, wherein R_1 is alkenyl or alkynyl.

4. A process according to any one of claims 1 to 3, wherein R_3 is alkyl or alkynyl.

5. A process for the production of a β-lactam of the formula:

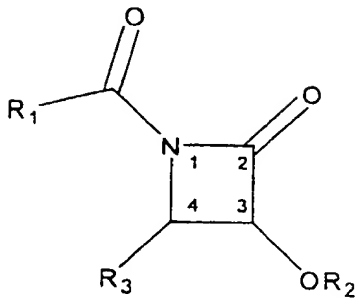


wherein R_2 is a hydroxyl protecting group, which comprises cyclocondensing an α-acyloxyacetyl chloride with an imine in the presence of a tertiary amine, said imine being the reaction product of benzaldehyde and p-methoxyaniline, to form a 1-p-methoxyphenyl-3-acyloxy-4-phenylazetidin-2-one, and removing the p-methoxyphenyl group by oxidation with ceric ammonium nitrate, followed by hydrolysis to convert the 3-acyloxy group to a 3-hydroxy group, and protecting the 3-hydroxy group thereby to convert it to a 3-OR_2 group.

6. A process according to any one of claims 1 to 5, wherein R_2 is selected from acetals, ethers, esters, and carbonates.

7. A process according to any one of claims 1 to 6, wherein R_2 is ethoxyethyl.

8. A process for the preparation of a taxol intermediate comprising contacting an alcohol with a β-lactam having the formula:



wherein

R_1 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido;
R_2 is a hydroxyl protecting group and
R_3 is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; and wherein any alkyl group present may be substituted or unsubstituted and contains from 1 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, any alkenyl or alkynyl group present may be substituted or unsubstituted and contains from 2 to 6 carbon atoms in the principal chain and up to 15 carbon atoms in total, and any aryl or substituted aryl group present contains from 6 to 15 carbon atoms; or an enantiomer or diastereoisomer thereof,
the contacting of said alcohol and β-lactam being carried out in the presence of a sufficient amount of an activating agent under effective conditions to cause the β-lactam to react with the alcohol to form a β-amido ester which is suitable for use as an intermediate in the synthesis of taxol.

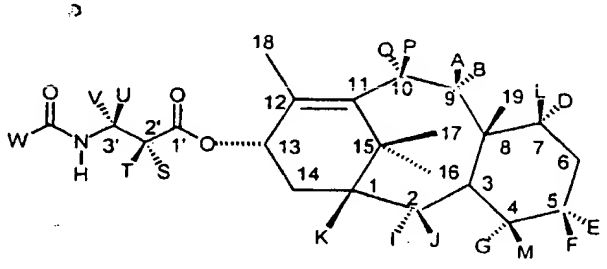
9. A process for the preparation of taxol which comprises preparing a taxol intermediate by a process according to claim 8 and converting said intermediate to taxol.

10. A process according to claim 8 or claim 9, wherein the hydroxyl protecting group is selected from acetals, ethers, esters, and carbonates.

11. A process according to any one of claims 8 to 10, wherein R_1 is aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl. aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; R_2 is ethoxyethyl or 2,2,2-trichloroethoxymethyl; and R_3 is aryl or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido.

12. A process according to any one of claims 8 to 11, wherein R_2 is ethoxyethyl.

13. A process for the preparation of a taxol having the formula:



wherein

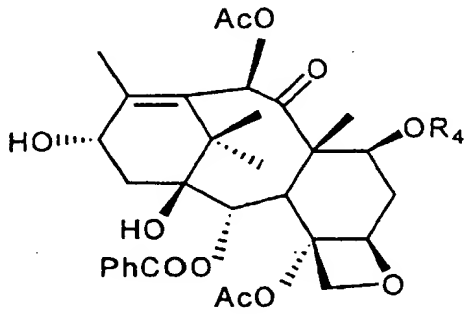
A and B are independently hydrogen or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
A and B together form an oxo;
L and D are independently hydrogen or hydroxy or lower alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy;

E and F are independently hydrogen or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or;
E and F together form an oxo;
G is hydrogen or hydroxy or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
G and M together form an oxo or methylene or
G and M together form an oxirane ring or
M and F together form an oxetane ring;
J is hydrogen, hydroxy, or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
I is hydrogen, hydroxy, or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; or
I and J taken together form an oxo; and
K is hydrogen, hydroxy or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy; and
P and Q are independently hydrogen or alkanoyloxy, alkenoyloxy, alkynoyloxy, or aryloyloxy or
P and Q together form an oxo;
S is hydroxy;
T is hydrogen;
U and V are independently hydrogen or alkyl, alkenyl, alkynyl, aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido; and
W is alkyl, alkenyl, alkynyl, aryl, or aryl substituted by at least one substituent selected from alkanoxy, hydroxy, halogen, alkyl, aryl, alkenyl, acyl, acyloxy, nitro, amino and amido;
and wherein any alkyl group present may be substituted or unsubstituted and contains from 1 to 6 carbon atoms in the principal chain and up to 10 carbon atoms in total, any alkenyl or alkynyl group present may be substituted or unsubstituted and contains from 2 to 6 carbon atoms in the principal chain and up to 10 carbon atoms in total, and any aryl or substituted aryl group present contains from 6 to 10 carbon atoms;

comprising:

contacting a β-lactam according to any one of claims 1 to 5 with an alcohol, the contacting of said β-lactam and said alcohol being carried out in the presence of a sufficient amount of an activating agent under effective conditions to cause the β-lactam to react with the alcohol to form a β-amido ester which is suitable for use as an intermediate in the synthesis of taxol, and converting said intermediate to taxol.

14. A process according to any one of claims 8 to 13, wherein the alcohol has the formula:



wherein R_4 is a hydroxyl protecting group, Ph is phenyl and Ac is acetyl.

15. A process according to claim 14, wherein R_4 is selected from ethers, esters, carbonates and silyl groups.

16. A process according to claim 14 or claim 15, wherein R_4 is ethoxyethyl, trimethyl silyl or triethyl silyl.

17. A process according to any one of claims 8 to 16, wherein said R_1 is phenyl and said R_3 is phenyl.

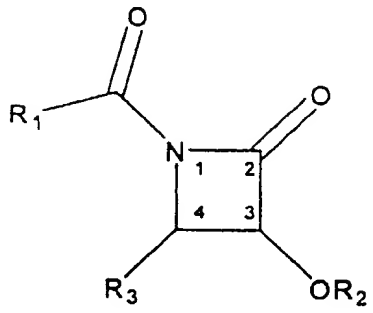
18. A process according to any one of claims 8 to 17, wherein the activating agent is a tertiary amine.

19. A process according to claim 18, wherein the activating agent is triethyl amine, diisopropyl ethyl amine, pyridine, N-methyl imidazole, or 4-dimethylaminopyridine.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten: AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. Ein β-Lactam der Formel:



1

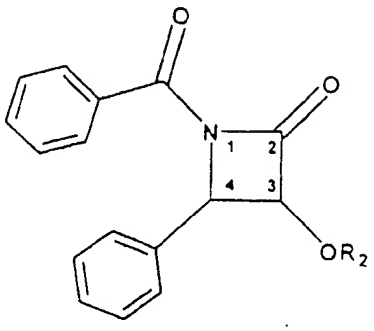
worin R_1 Alkyl, Alkenyl, Alkynyl, Aryl oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist; R_2 Ethoxyethyl, 2,2,2-Trichlorethoxymethyl oder eine andere Hydroxyl-Schutzgruppe ist; und R_3 Alkyl, Alkenyl, Alkynyl, Aryl, oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist; und in der irgendeine anwesende Alkylgruppe substituiert oder unsubstituiert sein kann und 1 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 15 Kohlenstoffatome insgesamt enthält, irgendeine anwesende Alkenyl- oder Alkynylgruppe substiuiert oder unsubstituiert sein kann und 2 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 15 Kohlenstoffatome insgesamt enthält, und irgendeine anwesende Aryl- oder substituierte Arylgruppe 6 bis 15 Kohlenstoffatome enthält; seine Enantiomeren und Diastereoisomeren.

2. Ein β-Lactam der Formel nach Anspruch 1, worin R_1 Phenyl, durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Phenyl oder Aryl ist; R_2 Ethoxyethyl oder 2,2,2-Trichlorethoxymethyl ist; und R_3 Phenyl, durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Phenyl oder Aryl ist.

3. Ein β-Lactam der Formel nach Anspruch 1 oder Anspruch 2, in dem R_2 Ethoxyethyl ist.

4. Ein β-Lactam nach einem der Ansprüche 1 bis 3, in dem R_1 Alkenyl oder Alkynyl ist.

5. Ein β-Lactam der Formel:

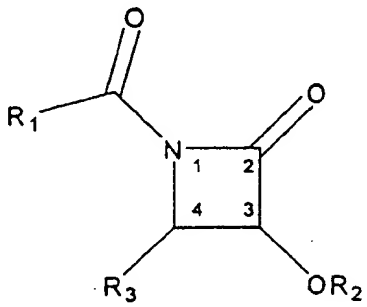


worin R_2 eine Hydroxyl-Schutzgruppe ist.

6. Ein β-Lactam nach einem der Ansprüche 1 bis 5, in dem R_2 unter Acetalen, Ethern, Estern und Carbonaten ausgewählt ist.

7. Ein β-Lactam nach einem der Ansprüche 1 bis 6, in dem R_3 Alkyl oder Alkynyl ist.

8. Ein Verfahren zur Herstellung eines Taxol-Zwischenprodukts, bei dem man einen Alkohol mit einem β-Lactam der Formel:



in Berührung bringt, worin

R_1 Alkyl, Alkenyl, Alkynyl, Aryl oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist;
R_2 eine Hydroxyl-Schutzgruppe ist und
R_3 Alkyl, Alkenyl, Alkynyl, Aryl, oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist; und worin irgendeine vorhandene Alkylgruppe substituiert oder unsubstituiert sein kann und 1 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 15 Kohlenstoffatome insgesamt enthält, irgendeine vorhandene Alkenyl- oder Alkynylgruppe substituiert oder unsubstituiert sein kann und 2 bis 6 Kohlenstoffatome in der Hauptkette und insgesamt bis zu 15 Kohlenstoffatome enthält, und irgendeine vorhandene Aryl- oder substituierte Arylgruppe 6 bis 15 Kohlenstoffatome enthält; oder seines Enantiomers oder Diastereoisomers,
wobei die Berührung des genannten Alkohols mit dem β-Lactam in Gegenwart einer ausreichenden Menge eines Aktivierungsmittels unter wirksamen Bedingungen erfolgt, um das β-Lactam zur Reaktion mit dem Alkohol unter Bildung eines β-Amidoesters zu veranlassen, der zur Verwendung als Zwischenprodukt in der Taxolsynthese geeignet ist.

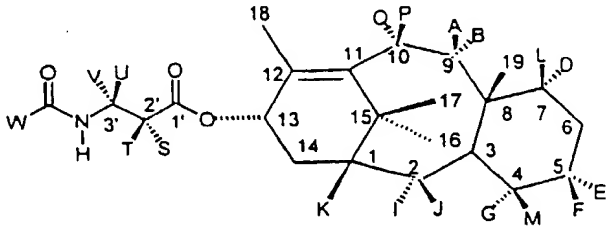
9. Verfahren zur Herstellung von Taxol, bei dem man ein Taxol-Zwischenprodukt durch ein Verfahren nach Anspruch 8 herstellt und das Zwischenprodukt zu Taxol umsetzt.

10. Verfahren nach Anspruch 8 oder Anspruch 9, bei dem man die Hydroxyl-Schutzgruppe unter Acetalen, Ethern, Estern und Carbonaten auswählt.

11. Verfahren nach einem der Ansprüche 8 bis 10, bei dem R_1 Aryl oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist; R_2 Ethoxyethyl oder 2,2,2-Trichlorethoxymethyl ist; und R_3 Aryl oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist.

12. Verfahren nach einem der Ansprüche 8 bis 11, bei dem R_2 Ethoxyethyl ist.

13. Ein Verfahren zur Herstellung eines Taxols mit der Formel:

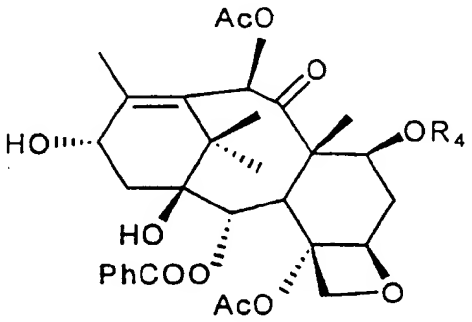


in der

A und B unabhängig Wasserstoff oder niederes Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy sind oder
A und B zusammen ein Oxo bilden;
L und D unabhängig Wasserstoff oder Hydroxy oder niederes Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy sind;
E und F unabhängig Wasserstoff oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy sind oder;
E und F zusammen ein Oxo bilden;
G Wasserstoff oder Hydroxy oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy ist oder
G und M zusammen ein Oxo oder Methylen bilden oder
G und M zusammen einen Oxiranring bilden oder
M und F zusammen einen Oxetanring bilden;
J Wasserstoff, Hydroxy oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy ist oder
I Wasserstoff, Hydroxy oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy ist; oder
I und J zusammen ein Oxo bilden; und
K Wasserstoff, Hydroxy oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy ist; und
P und Q unabhängig Wasserstoff oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy sind oder
P und Q zusammen ein Oxo bilden;
S Hydroxy ist;
T Wasserstoff ist;
U und V unabhängig Wasserstoff oder Alkyl, Alkenyl, Alkynyl, durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl sind; und
W Alkyl, Alkenyl, Alkynyl, Aryl, oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist;
und worin irgendeine anwesende Alkylgruppe substituiert oder unsubstituiert sein kann und 1 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 10 Kohlenstoffatome insgesamt enthält, irgendeine vorhandene Alkenyl- oder Alkynylgruppe substiuiert oder unsubstituiert sein kann und 2 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 10 Kohlenstoffatome insgesamt enthält, und irgendeine vorhandene Aryl- oder substituierte Arylgruppe 6 bis 10 Kohlenstoffatome enthält;
bei dem man ein β-Lactam nach einem der Ansprüche 1 bis 5 mit einem Alkohol in Kontakt bringt, die Kontaktierung des β-Lactams und des Alkohols in Gegenwart einer ausreichenden Menge eines Aktivierungsmittels unter wirksamen Bedingungen durchführt, um die Umsetzung des β-Lactams mit dem Alkohol zu einem

β-Amidoester zu veranlassen, der als Zwischenprodukt in der Taxolsynthese geeignet ist, und das genannte Zwischenprodukt zu Taxol umsetzt.

14. Ein Verfahren nach einem der Ansprüche 8 bis 13, bei dem der Alkohol die Formel:



hat, worin R_4 eine Hydroxyl-Schutzgruppe ist, Ph Phenyl ist und Ac Acetyl ist.

15. Verfahren nach Anspruch 14, bei dem R_4 unter Ethern, Estern, Carbonaten und Silylgruppen ausgewählt wird.

16. Verfahren nach Anspruch 14 oder Anspruch 15, bei dem R_4 Ethoxyethyl, Trimethylsilyl oder Triethylsilyl ist.

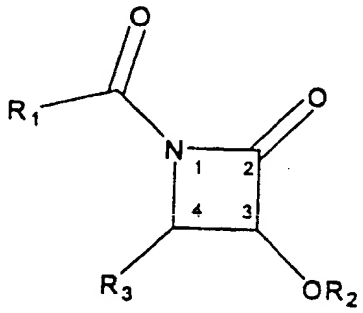
17. Verfahren nach einem der Ansprüche 8 bis 16, bei dem R_1 Phenyl ist und R_3 Phenyl ist.

18. Verfahren nach einem der Ansprüche 8 bis 17, bei dem das Aktivierungsmittel ein tertiäres Amin ist.

19. Verfahren nach Anspruch 18, bei dem das Aktivierungsmittel Triethylamin, Diisopropylethylamin, Pyridin, N-Methylimidazol oder 4-Dimethylaminopyridin ist.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Ein Verfahren zur Herstellung eines β-Lactams der Formel:



1

worin R_1 Alkyl, Alkenyl, Alkynyl, Aryl oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist; R_2 Ethoxyethyl, 2,2,2-Trichlorethoxymethyl oder eine andere Hydroxyl-Schutzgruppe ist; und R_3 Alkyl, Alkenyl, Alkynyl, Aryl, oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist; und worin irgendeine anwesende Alkylgruppe substituiert

oder unsubstituiert sein kann und 1 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 15 Kohlenstoffatome insgesamt enthält, irgendeine anwesende Alkenyl- oder Alkynylgruppe substiuiert oder unsubstituiert sein kann und 2 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 15 Kohlenstoffatome insgesamt enthält, und irgendeine anwesende Aryl- oder substituierte Arylgruppe 6 bis 15 Kohlenstoffatome enthält; seines Enantiomers oder Diastereoisomers,

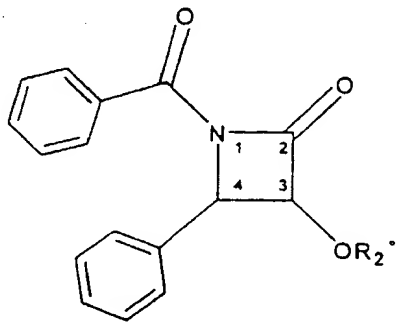
wobei man ein α-Acyloxyacetylchlorid mit einem Imin, welches das Reaktionsprodukt eines Aldehyds der Formel R_3CHO und p-Methoxyanilins ist, in Gegenwart eines tertiären Amins unter Bildung eines 1-p-Methoxyphenyl-3-Acyloxy-4-Arylazetidin-2-ons polykondensiert und die p-Methoxyphenylgruppe durch Oxidation mit Cerammoniumnitrat entfernt mit anschließender Hydrolyse zur Umsetzung der 3-Acyloxygruppe zu einer 3-Hydroxygruppe, und die 3-Hydroxygruppe schützt, um sie dadurch zu einer 3-OR_2-Gruppe umzusetzen.

2. Verfahren nach Anspruch 1, bei dem R_1 Phenyl, durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Phenyl oder Aryl ist; R_2 Ethoxyethyl oder 2,2,2-Trichlorethoxymethyl ist; und R_3 Phenyl, durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Phenyl oder Aryl ist.

3. Verfahren nach Anspruch 1 oder Anspruch 2, bei dem R_1 Alkenyl oder Alkynyl ist.

4. Verfahren nach einem der Ansprüche 1 bis 3, bei dem R_3 Alkyl oder Alkynyl ist.

5. Verfahren zur Herstellung eines β-Lactams der Formel:

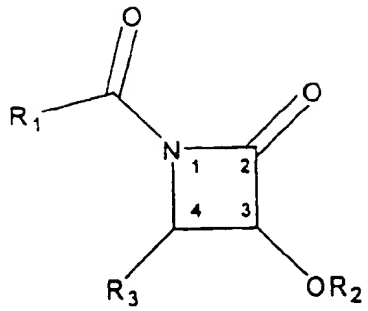


worin R_2 eine Hydroxyl-Schutzgruppe ist, bei dem man ein α-Acyloxyacetylchlorid mit einem Imin, das das Reaktionsprodukt von Benzaldehyd und p-Methoxyanilin ist, in Gegenwart eines tertiären Amins unter Bildung eines 1-p-Methoxyphenyl-3-Acyloxy-4-Phenylazetidin-2-ons polykondensiert und die p-Methoxyphenylgruppe durch Oxidation mit Cerammoniumnitrat entfernt mit nachfolgender Hydrolyse zur Umsetzung der 3-Acyloxygruppe zu einer 3-Hydroxygruppe, und die 3-Hydroxygruppe schützt, um sie dadurch zu einer 3-OR_2-Gruppe umzusetzen.

6. Verfahren nach einem der Ansprüche 1 bis 5, in dem R_2 unter Acetalen, Ethern, Estern und Carbonaten ausgewählt wird.

7. Verfahren nach einem der Ansprüche 1 bis 6, in dem R_2 Ethoxyethyl ist.

8. Verfahren zur Herstellung eines Taxol-Zwischenprodukts, bei dem man einen Alkohol mit einem β-Lactam der Formel:



umsetzt, worin

R_1 Alkyl, Alkenyl, Alkynyl, Aryl oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist;
R_2 eine Hydroxyl-Schutzgruppe ist und
R_3 Alkyl, Alkenyl, Alkynyl, Aryl, oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist; und worin irgendeine anwesende Alkylgruppe substituiert oder unsubstituiert sein kann und 1 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 15 Kohlenstoffatome insgesamt enthält, irgendeine anwesende Alkenyl- oder Alkynylgruppe substituiert oder unsubstituiert sein kann und 2 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 15 Kohlenstoffatome insgesamt enthält, und irgendeine anwesende Aryl- oder substituierte Arylgruppe 6 bis 15 Kohlenstoffatome enthält, oder seines Enantiomers oder Diastereoisomers,
wobei die Kontaktierung des Alkohols und β-Lactams in Gegenwart einer ausreichenden Menge eines Aktivierungsmittels unter wirksamen Bedingungen erfolgt, um die Reaktion des β-Lactams mit dem Alkohol unter Bildung eines β-Amidoesters zu veranlassen, der für den Einsatz als Zwischenprodukt in der Taxolsynthese geeignet ist.

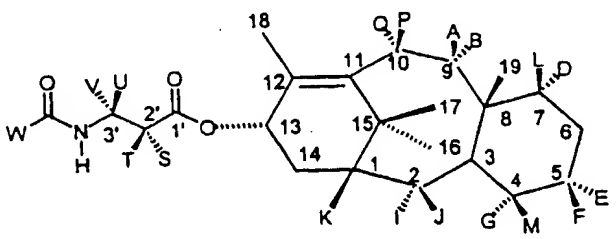
9. Verfahren zur Herstellung von Taxol, bei dem man ein Taxol-Zwischenprodukt durch ein Verfahren nach Anspruch 8 herstellt und das Zwischenprodukt zu Taxol umsetzt.

10. Verfahren nach Anspruch 8 oder Anspruch 9, bei dem man die Hydroxyl-Schutzgruppe unter Acetalen, Ethern, Estern und Carbonaten auswählt.

11. Verfahren nach einem der Ansprüche 8 bis 10, bei dem R_1 Aryl oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist; R_2 Ethoxyethyl oder 2,2,2-Trichlorethoxymethyl ist; und R_3 Aryl oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl ist.

12. Verfahren nach einem der Ansprüche 8 bis 11, bei dem R_2 Ethoxyethyl ist.

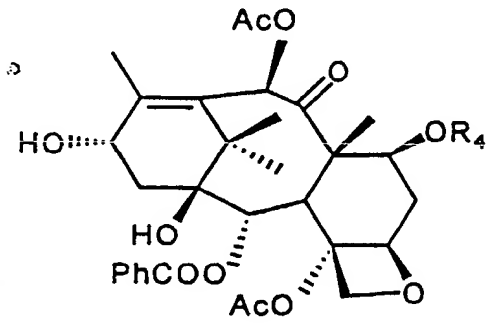
13. Ein Verfahren zur Herstellung eines Taxols mit der Formel:



in der

A und B unabhängig Wasserstoff oder niederes Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy sind oder
A und B zusammen ein Oxo bilden;
L und D unabhängig Wasserstoff oder Hydroxy oder niederes Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy sind;
E und F unabhängig Wasserstoff oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy sind oder;
E und F zusammen ein Oxo bilden;
G Wasserstoff oder Hydroxy oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy ist oder
G und M zusammen ein Oxo oder Methylen bilden oder
G und M zusammen einen Oxiranring bilden oder
M und F zusammen einen Oxetanring bilden;
J Wasserstoff, Hydroxy oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy ist oder
I Wasserstoff, Hydroxy oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy ist; oder
I und J zusammengenommen ein Oxo bilden; und
K Wasserstoff, Hydroxy oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy ist; und
P und Q unabhängig Wasserstoff oder Alkanoyloxy, Alkenoyloxy, Alkynoyloxy oder Aryloyloxy sind oder
P und Q zusammen ein Oxo bilden;
S Hydroxy ist;
T Wasserstoff ist;
U und V unabhängig Wasserstoff oder Alkyl, Alkenyl, Alkynyl, durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido substituiertes Aryl sind; und
W Alkyl, Alkenyl, Alkynyl, Aryl oder durch wenigstens einen Substituenten ausgewählt unter Alkanoxy, Hydroxy, Halogen, Alkyl, Aryl, Alkenyl, Acyl, Acyloxy, Nitro, Amino und Amido ausgewähltes Aryl ist;
und worin irgendeine anwesende Alkylgruppe substituiert oder unsubstituiert sein kann und 1 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 10 Kohlenstoffatome insgesamt enthält, irgendeine vorhandene Alkenyl- oder Alkynylgruppe substiuiert oder unsubstituiert sein kann und 2 bis 6 Kohlenstoffatome in der Hauptkette und bis zu 10 Kohlenstoffatome insgesamt enthält, und irgendeine anwesende Aryl- oder substituierte Arylgruppe 6 bis 10 Kohlenstoffatome enthält;
bei dem man ein β-Lactam nach einem der Ansprüche 1 bis 5 mit einem Alkohol in Kontakt bringt, wobei die Kontaktierung des β-Lactams und des Alkohols in Gegenwart einer ausreichenden Menge eines Aktivierungsmittels unter wirksamen Bedingungen durchführt wird, um das β-Lactam zur Umsetzung mit dem Alkohol unter Bildung eines β-Amidoester zu veranlassen, der für den Einsatz als Zwischenprodukt in der Taxolsynthese geeignet ist, und das genannte Zwischenprodukt zu Taxol umsetzt.

14. Verfahren nach einem der Ansprüche 8 bis 13, bei dem der Alkohol die Formel:



hat, worin R_4 eine Hydroxyl-Schutzgruppe ist, Ph Phenyl ist und Ac Acetyl ist.

15. Verfahren nach Anspruch 14, bei dem R_4 unter Ethern, Estern, Carbonaten und Silylgruppen ausgewählt wird.

16. Verfahren nach Anspruch 14 oder Anspruch 15, bei dem R_4 Ethoxyethyl, Trimethylsilyl oder Triethylsilyl ist.

17. Verfahren nach einem der Ansprüche 8 bis 16, bei dem das R_1 Phenyl ist und das R_3 Phenyl ist.

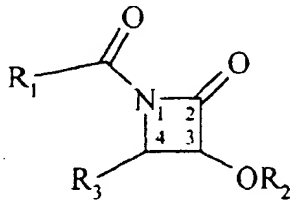
18. Verfahren nach einem der Ansprüche 8 bis 17, bei dem das Aktivierungsmittel ein tertiäres Amin ist.

19. Verfahren nach Anspruch 18, bei dem das Aktivierungsmittel Triethylamin, Diisopropylethylamin, Pyridin, N-Methylimidazol oder 4-Dimethylaminopyridin ist.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, LI, DE, DK, FR, GB, IT, LU, NL, SE

1. β-lactame de la formule



I

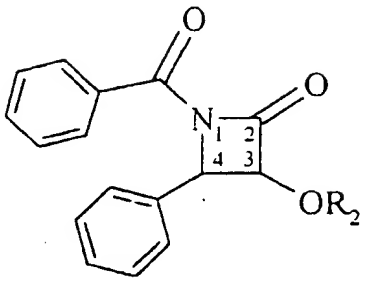
dans laquelle R_1 est un groupe alkyle, alcényle, alkynyle, aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido; R_2 est un groupe éthoxyéthyle, 2,2,2-trichloroéthoxyméthyle ou un autre groupe bloquant un groupe hydroxyle; et R_3 est un groupe alkyle, alcényle, alkynyle, aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido; et dans lequel tout groupe alkyle présent peut être substitué ou non substitué et contient de 1 à 6 atomes de carbone dans la chaîne principale et jusqu'à 15 atomes de carbone au total, tout groupe alcényle ou alkynyle présent peut être substitué ou non substitué et contient de 2 à 6 atomes de carbone dans la chaîne principale et jusqu'à 15 atomes de carbone au total, et tout groupe aryle ou aryle substitué présent contient de 6 à 15 atomes de carbone; des énantiomères et des diastéréoisomères de celui-ci.

2. β-lactame selon la revendication 1, dans lequel R_1 est un groupe phényle, phényle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido, ou aryle; R_2 est un groupe éthoxyéthyle ou 2,2,2-trichloroéthoxyméthyle; et R_3 est un groupe phényle, phényle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido, ou aryle.

3. β-lactame selon la revendication 1 ou la revendication 2, dans lequel R_2 est le groupe éthoxyéthyle.

4. β-lactame selon l'une quelconque des revendications 1 à 3, dans lequel R_1 est un groupe alcényle ou alkynyle.

5. β-lactame de la formule

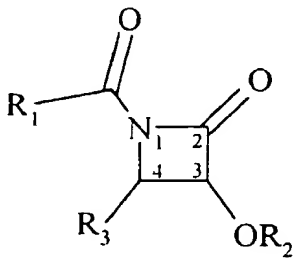


dans laquelle R_2 est un groupe bloquant un groupe hydroxyle.

6. β-lactame selon l'une quelconque des revendications 1 à 5, dans lequel R_2 est choisi parmi des acétals, des éthers, des esters et des carbonates.

7. β-lactame selon l'une quelconque des revendications 1 à 6, dans lequel R_3 est un groupe alkyle ou alkynyle.

8. Procédé pour la préparation d'un intermédiaire de taxol comprenant la mise en contact d'un alcool avec un β-lactame présentant la formule :



dans laquelle

R_1 est un groupe alkyle, alcényle, alkynyle, aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido;
R_2 est un groupe bloquant un groupe hydroxyle et
R_3 est un groupe alkyle, alcényle, alkynyle, aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido; et dans lequel tout groupe alkyle présent peut être substitué ou non substitué et contient de 1 à 6 atomes de carbone dans la chaîne principale et jusqu'à 15 atomes de carbone au total, tout groupe alcényle ou alkynyle présent peut être substitué ou non substitué et contient de 2 à 6 atomes de carbone dans la chaîne principale et jusqu'à 15 atomes de carbone au total, et tout groupe aryle ou aryle substitué présent contient de 6 à 15 atomes de carbone; ou avec un énantiomère ou un diastéréoisomère de celui-ci,
la mise en contact desdits alcool et β-lactame étant réalisée en présence d'une quantité suffisante d'un agent d'activation dans des conditions efficaces pour faire en sorte que le β-lactame réagisse avec l'alcool pour former un β-amido-ester qui est utilisable comme intermédiaire dans la synthèse de taxol.

9. Procédé pour la préparation de taxol qui comprend la préparation d'un intermédiaire de taxol par un procédé selon la revendication 8 et la transformation dudit intermédiaire en taxol.

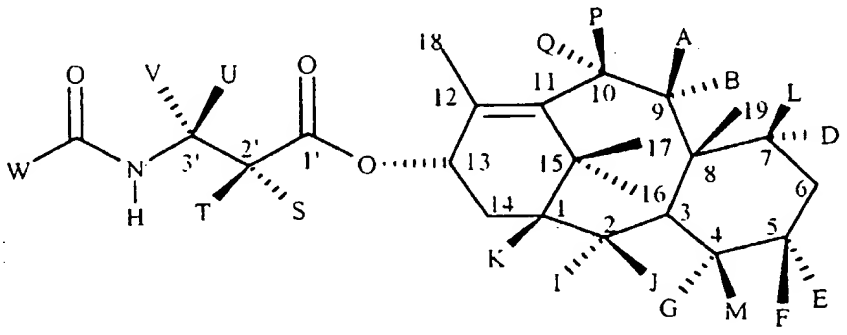
10. Procédé selon la revendication 8 ou la revendication 9, dans lequel le groupe bloquant un groupe hydroxyle est choisi parmi des acétals, d s éthers, des sters et des carbonates.

11. Procédé selon l'une quelconque des revendications 8 à 10, dans lequel R_1 est un groupe aryle ou aryle substitué

par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido; R_2 est un groupe éthoxyéthyle ou 2,2,2-trichloroéthoxyméthyle, et R_3 est un groupe aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido.

12. Procédé selon l'une quelconque des revendications 8 à 11, dans lequel R_2 est le groupe éthoxyéthyle.

13. Procédé pour la préparation d'un taxol présentant la formule :



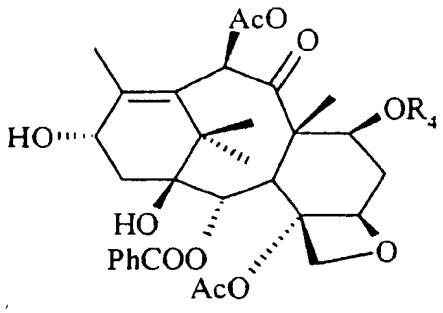
dans laquelle

A et B sont indépendamment un atome d'hydrogène ou un groupe alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy inférieur ou
A et B forment ensemble un groupe oxo;
L et D sont indépendamment un atome d'hydrogène ou un groupe hydroxy ou alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy inférieur;
E et F sont indépendamment un atome d'hydrogène ou un groupe alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy ou;
E et F forment ensemble un groupe oxo;
G est un atome d'hydrogène ou un groupe hydroxy ou alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy ou
G et M forment ensemble un groupe oxo ou méthylène ou
G et M forment ensemble un noyau oxyrane ou
M et F forment ensemble un noyau oxétanne;
J est un atome d'hydrogène, un groupe hydroxy, ou alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy ou
I est un atome d'hydrogène, un groupe hydroxy, ou alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy; ou
I et J pris ensemble forment un groupe oxo; et
K est un atome d'hydrogène, un groupe hydroxy ou alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy; et
P et Q sont indépendamment un atome d'hydrogène ou un groupe alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy ou
P et Q forment ensemble un groupe oxo;
S est un groupe hydroxy;
T est un atome d'hydrogène;
U et V sont indépendamment un atome d'hydrogène ou un groupe alkyle, alcényle, alkynyle, aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido; et
W est un groupe alkyle, alcényle, alkynyle, aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido;
et dans lequel tout groupe alkyle présent peut être substitué ou non substitué et contient de 1 à 6 atomes de carbone dans la chaîne principale et jusqu'à 10 atomes de carbone au total, tout groupe alcényle ou alkynyle présent peut être substitué ou non substitué et contient de 2 à 6 atomes de carbone dans la chaîne principale et jusqu'à 10 atomes de carbone au total et tout groupe aryle ou aryle substitué présent contient de 6 à 10 atomes de carbone;

comprenant :

la mise en contact d'un β-lactame selon l'une quelconque des revendications 1 à 5 avec un alcool, la mise en contact dudit β-lactame et dudit alcool étant réalisée en présence d'une quantité suffisante d'un agent d'activation dans des conditions efficaces pour faire en sorte que le β-lactame réagisse avec l'alcool pour former un β-amido-ester qui est utilisable comme intermédiaire dans la synthèse de taxol et la transformation dudit intermédiaire en taxol.

14. Procédé selon l'une quelconque des revendications 8 à 13, dans lequel l'alcool présente la formule :



dans laquelle R_4 est un groupe bloquant un groupe hydroxyle, Ph est le groupe phényle et Ac est le groupe acétyle.

15. Procédé selon la revendication 14, dans lequel R_4 est choisi parmi des éthers, des esters, des carbonates et des groupes silyle.

16. Procédé selon la revendication 14 ou la revendication 15, dans lequel R_4 est le groupe éthoxyéthyle, triméthylsilyle ou triéthylsilyle.

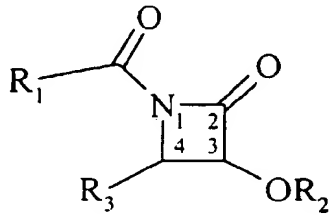
17. Procédé selon l'une quelconque des revendications 8 à 16, dans lequel ledit R_1 est le groupe phényle et ledit R_3 est le groupe phényle.

18. Procédé selon l'une quelconque des revendications 8 à 17, dans lequel l'agent d'activation est une amine tertiaire

19. Procédé selon la revendication 18, dans lequel l'agent d'activation est la triéthylamine, la diisopropyléthylamine, la pyridine, le N-méthylimidazole ou la 4-diméthylaminopyridine.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la production d'un β-lactame de la formule :



I

dans laquelle R_1 est un groupe alkyle, alcényle, alkynyle, aryle ou aryle substitué par au moins un substituant

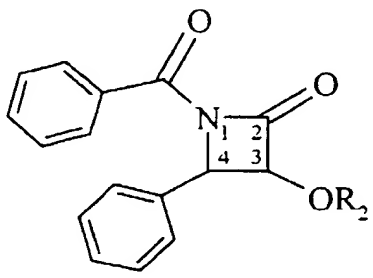
choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido; R_2 est un groupe éthoxyéthyle, 2,2,2-trichloroéthoxyméthyle ou un autre groupe bloquant un groupe hydroxyle; et R_3 est un groupe alkyle, alcényle, alkynyle, aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido; et dans lequel tout groupe alkyle présent peut être substitué ou non substitué et contient de 1 à 6 atomes de carbone dans la chaîne principale et jusqu'à 15 atomes de carbone au total, tout groupe alcényle ou alkynyle présent peut être substitué ou non substitué et contient de 2 à 6 atomes de carbone dans la chaîne principale et jusqu'à 15 atomes de carbone au total, et tout groupe aryle ou aryle substitué présent contient de 6 à 15 atomes de carbone, d'un énantiomère ou d'un diastéréoisomère de celui-ci, lequel procédé comprend la cyclocondensation d'un chlorure de α-acyloxyacétyle avec une imine en présence d'une amine tertiaire, ladite imine étant le produit de la réaction d'un aldéhyde de formule R_1CHO et de p-méthoxyaniline pour former une 1-p-méthoxyphényl-3-acyloxy-4-arylazétidin-2-one, et l'élimination du groupe p-méthoxyphényle par oxydation avec du nitrate d'ammonium cérique, suivie par une hydrolyse pour transformer le groupe 3-acyloxy en un groupe 3-hydroxy et le blocage du groupe 3-hydroxy pour le transformer par là en un groupe 3-OR_2.

2. Procédé selon la revendication 1, dans lequel R_1 est un groupe phényle, phényle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido, ou aryle; R_2 est un groupe éthoxyéthyle ou 2,2,2-trichloroéthoxyméthyle; et R_3 est un groupe phényle, phényle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido, ou aryle.

3. Procédé selon la revendication 1 ou la revendication 2, dans lequel R_1 est un groupe alcényle ou alkynyle.

4. Procédé selon l'une quelconque des revendications 1 à 3, dans lequel R_3 est un groupe alkyle ou alkynyle.

5. Procédé pour la production d'un β-lactame de la formule :

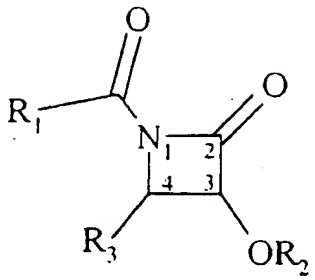


dans laquelle R_2 est un groupe bloquant un groupe hydroxyle, lequel comprend la cyclocondensation d'un chlorure de α-acyloxyacétyle avec une imine en présence d'une amine tertiaire, ladite imine étant le produit de la réaction de benzaldéhyde et de p-méthoxyaniline pour former une 1-p-méthoxyphényl-3-acyloxy-4-phénylazétidin-2-one, et l'élimination du groupe p-méthoxyphényle par oxydation avec du nitrate d'ammonium cérique, suivie par une hydrolyse pour transformer le groupe 3-acyloxy en un groupe 3-hydroxy et le blocage du groupe 3-hydroxy pour le transformer par là en un groupe 3-OR_2.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel R_2 est choisi parmi des acétals, des éthers, des esters et des carbonates.

7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel R_2 est le groupe éthoxyéthyle.

8. Procédé pour la préparation d'un intermédiaire de taxol comprenant la mise en contact d'un alcool avec un β-lactame présentant la formule :



dans laquelle

R_1 est un groupe alkyle, alcényle, alkynyle, aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido;
R_2 est un groupe bloquant un groupe hydroxyle et
R_3 est un groupe alkyle, alcényle, alkynyle, aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido; et dans lequel tout groupe alkyle présent peut être substitué ou non substitué et contient de 1 à 6 atomes de carbone dans la chaîne principale et jusqu'à 15 atomes de carbone au total, tout groupe alcényle ou alkynyle présent peut être substitué ou non substitué et contient de 2 à 6 atomes de carbone dans la chaîne principale et jusqu'à 15 atomes de carbone au total, et tout groupe aryle ou aryle substitué présent contient de 6 à 15 atomes de carbone; ou avec un énantiomère ou un diastéréoisomère de celui-ci,
la mise en contact desdits alcool et β-lactame étant réalisée en présence d'une quantité suffisante d'un agent d'activation dans des conditions efficaces pour faire en sorte que le β-lactame réagisse avec l'alcool pour former un β-amido-ester qui est utilisable comme intermédiaire dans la synthèse de taxol.

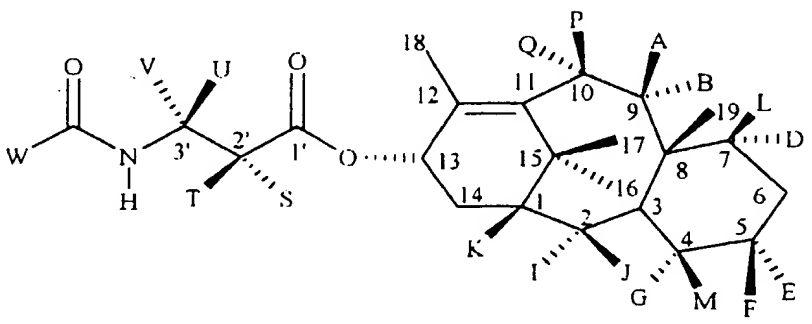
9. Procédé pour la préparation de taxol qui comprend la préparation d'un intermédiaire de taxol par un procédé selon la revendication 8 et la transformation dudit intermédiaire en taxol.

10. Procédé selon la revendication 8 ou la revendication 9, dans lequel le groupe bloquant un groupe hydroxyle est choisi parmi des acétals, des éthers, des esters et des carbonates.

11. Procédé selon l'une quelconque des revendications 8 à 10, dans lequel R_1 est un groupe aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido; R_2 est un groupe éthoxyéthyle ou 2,2,2-trichloroéthoxyméthyle; et R_3 est un groupe aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido.

12. Procédé selon l'une quelconque des revendications 8 à 11, dans lequel R_2 est le groupe éthoxyéthyle.

13. Procédé pour la préparation d'un taxol présentant la formule :



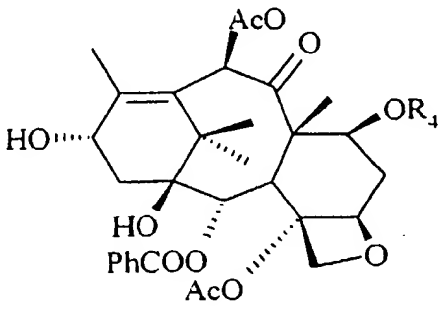
dans laquelle

A et B sont indépendamment un atome d'hydrogène ou un groupe alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy inférieur ou
A et B forment ensemble un groupe oxo;
L et D sont indépendamment un atome d'hydrogène ou un groupe hydroxy ou alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy inférieur;
E et F sont indépendamment un atome d'hydrogène ou un groupe alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy ou;
E et F forment ensemble un groupe oxo;
G est un atome d'hydrogène ou un groupe hydroxy ou alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy ou
G et M forment ensemble un groupe oxo ou méthylène ou
G et M forment ensemble un noyau oxyrane ou
M et F forment ensemble un noyau oxétanne;
J est un atome d'hydrogène, un groupe hydroxy, ou alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy ou
I est un atome d'hydrogène, un groupe hydroxy, ou alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy; ou
I et J pris ensemble forment un groupe oxo; et
K est un atome d'hydrogène, un groupe hydroxy ou alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy; et
P et Q sont indépendamment un atome d'hydrogène ou un groupe alcanoyloxy, alcénoyloxy, alkynoyloxy ou aryloyloxy ou
P et Q forment ensemble un groupe oxo;
S est un groupe hydroxy;
T est un atome d'hydrogène;
U et V sont indépendamment un atome d'hydrogène ou un groupe alkyle, alcényle, alkynyle, aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido; et
W est un groupe alkyle, alcényle, alkynyle, aryle ou aryle substitué par au moins un substituant choisi parmi un groupe alcanoxy, hydroxy, un atome d'halogène, un groupe alkyle, aryle, alcényle, acyle, acyloxy, nitro, amino et amido;
et dans lequel tout groupe alkyle présent peut être substitué ou non substitué et contient de 1 à 6 atomes de carbone dans la chaîne principale et jusqu'à 10 atomes de carbone au total, tout groupe alcényle ou alkynyle présent peut être substitué ou non substitué et contient de 2 à 6 atomes de carbone dans la chaîne principale et jusqu'à 10 atomes de carbone au total et tout groupe aryle ou aryle substitué présent contient de 6 à 10 atomes de carbone;

comprenant :

la mise en contact d'un β-lactame selon l'une quelconque des revendications 1 à 5 avec un alcool, la mise en contact dudit β-lactame et dudit alcool étant réalisée en présence d'une quantité suffisante d'un agent d'activation dans des conditions efficaces pour faire en sorte que le β-lactame réagisse avec l'alcool pour former un β-amido-ester qui est utilisable comme intermédiaire dans la synthèse de taxol et la transformation dudit intermédiaire en taxol.

14. Procédé selon l'une quelconque des revendications 8 à 13, dans lequel l'alcool présente la formule :



dans laquelle R_4 est un groupe bloquant un groupe hydroxyle, Ph est le groupe phényle et Ac est le groupe acétyle.

15. Procédé selon la revendication 14, dans lequel R_4 est choisi parmi des éthers, des esters, des carbonates et des groupes silyle.

16. Procédé selon la revendication 14 ou la revendication 15, dans lequel R_4 est un groupe éthoxyéthyle, triméthylsilyle ou triéthylsilyle.

17. Procédé selon l'une quelconque des revendications 8 à 16, dans lequel ledit R_1 est le groupe phényle et ledit R_3 est le groupe phényle.

18. Procédé selon l'une quelconque des revendications 8 à 17, dans lequel l'agent d'activation est une amine tertiaire.

19. Procédé selon la revendication 18, dans lequel l'agent d'activation est la triéthylamine, la diisopropyléthylamine, la pyridine, le N-méthylimidazole ou la 4-diméthylaminopyridine.

(19) Europäisches Patentamt
European Patent Office
Office europé n des brevets

(11) Publication number: **0 400 971 A3**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **90305845.1**

(51) Int. Cl.5: **C07D 205/08**, C07D 305/14

(22) Date of filing: **30.05.90**

(30) Priority: **31.05.89 US 359634**
29.09.89 US 415028

(43) Date of publication of application:
05.12.90 Bulletin 90/49

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(88) Date of deferred publication of the search report:
02.01.92 Bulletin 92/01

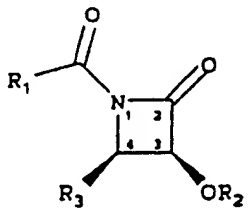
(71) Applicant: **FLORIDA STATE UNIVERSITY**
2035 East Paul Dirac Drive
Tallahassee, Florida(US)

(72) Inventor: **Holton, Robert A**
2731 Blairstone Road 165
Tallahassee, Florida(US)

(74) Representative: **Eyles, Christopher Thomas et al**
W.P. THOMPSON & CO. High Holborn House
52-54 High Holborn
London WC1V 6RY(GB)

(54) **Method for preparation of taxol.**

(57) A β-lactam of the formula:



wherein R_1 is aryl, substituted aryl, alkyl, alkenyl, or alkynyl; R_2 is hydrogen, alkyl, acyl, acetal, ethoxyethyl, or other hydroxyl protecting group; and R_3 is aryl, substituted aryl, alkyl, alkenyl, or alkynyl; and process for the preparation of taxol comprising contacting said β-lactam and an alcohol in the presence of an activating agent to provide a taxol intermediate, and converting the intermediate to taxol.

EP 0 400 971 A3

Europ an Patent Offic

EUROPEAN SEARCH REPORT

Application Number

EP 90 30 5845

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 110, 1988, pages 5.917-5.919, Washington, US; J.-N. DENIS et al.: "A highly efficient, practical approach to natural taxol" * Pages 5.917-5.918 *	1,11,12	C 07 D 205/08 C 07 D 305/14

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C 07 D 205/00
C 07 D 305/00

The present search report has been drawn up for all claims

Place of search	Date of completion of search	Examiner
The Hague	29 October 91	FRANCOIS J.C.L.

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same catagory
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention

E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document